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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,417	01/07/2002	Michele Pagano	5914-090-999	1343

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,417	PAGANO, MICHELE	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4 and 7 have been amended. Claims 1-9 are pending and under consideration.

The rejection of claims 1-9 under 112, second paragraph is maintained for reasons of record. Claims 1, 4 and 7 recite the limitation of "detecting a change in the activity of skp2". The metes and bounds of the activity of skp2 is not defined by the specification. The specification states that skp2 has ubiquitination ligase activity, and that skp2 associates with skp2-specific substrates and Skp2 interacts with cell cycle regulators such as p27. The claims are vague and indefinite as Skp2 has associations with numerous proteins within the cell as well as ubiquitin-ligase activity.

Applicant argues that the specification sites numerous activities of Skp2 on page 50, line 17 to page 51, line 30. This has been considered but not found persuasive. The examples of Skp2 activity provided in the specification are specific embodiments; said examples do not constitute a limiting definition for Skp2 activity.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al, PNAS, 1998, Vol. 95, pp. 11324-11329, cited in the previous Office action) in view of Amati et al (Nature Cell Biology, 1999, Vol. 1, pp. E91-E93).

Claim 1 is drawn to a method for screening compounds useful for the treatment of proliferate and differentiative disorders comprising contacting a compound with a cell or a cell extract expressing Cks1 and Skp2, or Cks1, p27 and Skp2, and detecting a change in the activity of Skp2. Claim 2 embodies the method of claim 1 wherein the change in the activity of Skp2 is detected by detecting a change in the interaction of Skp2 with either p27 or Cks1. Claim 3 embodies the method of claim 1 wherein the change in the activity of Skp2 is detected by detecting a change in the ubiquitination of p27 or degradation of p27 or Cks 1. Claim 4 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound in a purified system containing Cks1 and Skp2, or Cks1, p27 and Skp2, and detecting a change in the activity of Skp2. Claim 5 embodies the method of claim 4 wherein the change in the activity of Skp2 is detected by detecting a change in the interaction of Skp2 with either p27or Cks1. Claim 6 embodies the method of claim 4 wherein the change in the activity of Skp2 is detected by detecting a change in the ubiquitination

of p27 or degradation of p27 or Cks1. Claim 7 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound in a purified system containing Skp2 and one or both of a polypeptide corresponding to the carboxyl terminus of the human p27 chain having the sequence NAGSVEWTPKKPGLRRRQT (SEQ ID NO:91) with or without a phosphothreonine at position 187 and Cks1, and detecting a change in the activity of Skp2. Claim 8 embodies the method of claim 7 wherein the change in the activity of Skp2 is detected by detecting a change in the interaction of Skp2 with either the polypeptide or Cks1. Claim 9 embodies the method of claim 7 wherein the change in the activity of Skp2 is detected by detecting a change in the ubiquitination of the polypeptide or degradation of the polypeptide or Cks1.

Yu et al teach that the complex comprising Skp1/Skp2/Cul-1 is likely to function as an E3 ligase to selectively target cyclin D and p21 for the ubiquitin dependent protein degradation, and that aberrant expression of skp1/Skp2/Cul-1 complex may contribute to tumorigenesis by regulating the level of G1 cell cycle regulators.

Amati et al (Nature Cell Biology, 1999, Vol. 1, pp. E91-E93) teach that SKP2 specifically associates with the peptide derived from the extreme carboxyl terminus of p27, in addition to full length p27 (page E91, second column, lines 27-31). Amati et al teach that Skp2 is required for degradation of p27 in vivo (page E91, third column, lines 29-32). Amati et al teach that in light of the available evidence it is likely that Shp2 is the substrate –recognition subunit of a p27-ubiquitin-ligase (page E91 to E92, bridging sentence). Amati et al teach that Skp2 promotes p27 degradation and accumulation of cyclin A (page E91, lines 44-46). Amati et al suggests that Skp2 allows the ubiquitination of p27kip1, E2F-1 and almost certainly other, as yet unknown substrates to be marked for degradation (page E92, second column, lines 58-60). Amati et al further suggest that it is necessary to determine if the SCFskp2 mediated degradation of p27 is directly regulated by extracellular stimuli, or is a secondary, but required consequence of G1 progression and CDK2 activation. Amati et al further suggest that SCFshp2 may interact with other proteins that control p27 function, such as c-Myc, D-type cyclins, Ras, Jab1, and possibly tumor suppressors such as VHL, PTEN, and Tsc-2 (page E93, first column, lines 2-13).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to screen compounds for the treatment of proliferative and

differentiative disorders comprising contacting a compound with a cell or a cell extract expressing Cul-1 and Skp2, or Cul1, p27 and Skp2 and detecting the degradation of p27 or cell cycle progression or inhibition.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Yu et al on the contribution of the Skp1/Skp2/Cul-1 complex on tumorigenesis, the teachings and suggestions of Amati et al regarding the governing interaction between Shp-2 and the degradation of p27 and entry into the cell cycle.. One of skill in the art would be motivated to find said compounds in order to treat malignant cells having defective control over the p27 pathway controlling the cell cycle.

All other rejections and objections as set forth in the previous Offide action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER

Karen A. Canella, Ph.D.
05/16/2004